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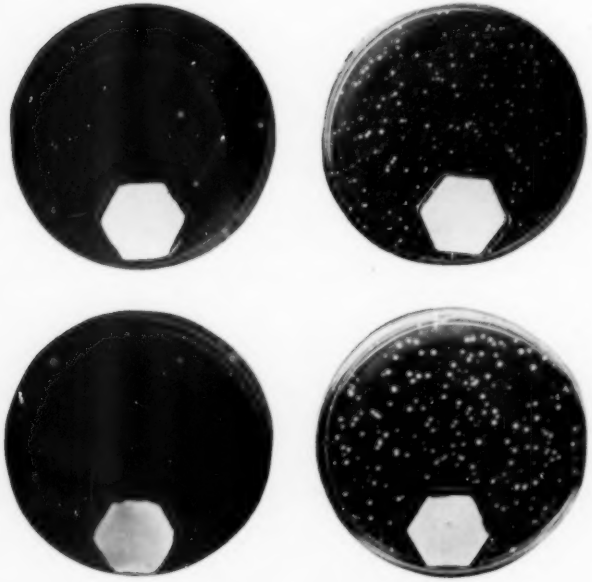

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American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription $4.00 — Foreign Postage, 25 Cents Extra
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EDITORIAL

THE STATUS OF HEROIN IN GREAT BRITAIN

THE current controversy taking place in Great Britain on the ban of the manufacture and sale of heroin makes interesting reading. Medical and pharmaceutical journals in recent months have devoted considerable space to this debate which may seem surprising to us in America where the manufacture of heroin has been prohibited for many years. On the other hand, some of the logic and philosophy expressed by our friends overseas is worthy of attention for, only too often today, we are apt to jump to conclusions and enact certain things into law where the result we expect to achieve is not likely to be accomplished. This seems to be the chief basis for the objections expressed in Britain to this action.

It is claimed that in Britain little or no heroin addiction exists and that it seems unreasonable to prohibit a drug considered by many physicians to be quite useful simply because many people are addicted to this drug in the United States. The question is raised whether this action by the British Government will in any way influence either addiction in the United States or the illicit supplies of this drug which are smuggled in here. To us, this seems an entirely sound piece of logic.

We do of course agree with those who argue that heroin possesses no particular virtue over other potent analgesics, and that its addiction potential is greater than any other potent analgesic. This in itself may warrant its ban in therapeutics.

In facing the entire narcotics problem, it is only too often that our authorities are forced to take many steps which they realize do little to attack the real root of the trouble. As almost everyone in this country who studies the problem must realize, practically all of the morphine and heroin used by addicts is illicit from the standpoint of its source. It is not imported through regular channels and, consequently, all of the regulations pertaining to pharmacists, physicians, and others permitted under law to handle narcotics accomplish very

little in eliminating addiction, even though these regulations are quite in order and need to be strictly enforced.

If one goes back to the primary cause of drug addiction in the world, it is because much more opium is grown than is required to meet the legitimate needs of medicine. It seems well established that the illicit supply of opium and opium alkaloids far exceeds that which is distributed through legal channels. This fact has been pinpointed by the United Nations many times but, as in other things, the United Nations is powerless to act unless its members themselves take certain steps within their own borders.

It is known the world over that the United States constitutes the most lucrative place to dispose of morphine and heroin since addiction here is common and the drug commands an exorbitant price. It is also true that our Bureau of Narcotics is grossly understaffed and that the chances of getting the drug into the country are quite good. While Congress makes quite a hue and cry about narcotic addiction, it does not see fit to give the necessary financial support to that agency entrusted with its eradication.

To go back to the issue faced by our British colleagues, we think their point is well taken for it seems to us extremely doubtful whether their ban on heroin will contribute to any degree toward the solution of our addiction problem. We know full well the sources of our illicit narcotics and they do not include the British Isles. Unfortunately, neither we, nor the United Nations, seem to be in a very good position to dry up the source and those countries which are involved seem either unwilling or unable to stem this tide.

L. F. Tice

SELECTED NEWER DEVELOPMENTS IN THE EVALUATION OF GERMICIDES *

(Part I)

By Emil G. Klarmann **

Introduction

WHEN the chairman of the Committee on Analytical Microbiology very kindly invited me to participate in this symposium, he assigned to me as discussion topic "the testing of disinfectants and antiseptics". At the same time, he indicated that the broader aspects of analysis and interpretation rather than a specific discussion of methodology was desired.

To do justice to such an assignment, within the short period of time at my disposal, would be a formidable task indeed. Actually, I feel that under these conditions the topic cannot be covered with any degree of adequacy. This is why only some selected facets of this matter can be reviewed within the framework of my presentation which, of necessity, will have to be entirely subjective in character.

While bacteriological testing of disinfectants and antiseptics has several points in common, it is deemed preferable to discuss the two subjects separately, for a variety of reasons.

Disinfectants

As to disinfectants, let it be said first that this is not considered to be the place for a complete history of the methodology of their evaluation. With specific reference to the methods in use within the recent past and up to the present, it seems logical to point to the original work of Rideal and Walker (1) who were the first to recognize the need for standardizing a number of experimental conditions as a means of insuring consistency of results. The Rideal-Walker method has been revised several times, both here and in Great Britain (*2-7*); moreover, its application has been extended to a considerable

* Presented at the Symposium on Analytical Microbiology, 56th General Meeting of the Society of American Bacteriologists, Houston, Texas, May 3, 1956.

** Lehn & Fink, Inc., New York, N. Y.

number of antibacterial products and processes, in some instances rationally, in others irrationally.

The most recent version is known as the "A. O. A. C. Phenol Coefficient Method" which, with the attribute "official", appears in the 1955 edition of the "Official Methods of Analysis", published by the "Association of Official Agricultural Chemists" (8). It provides, among other things, for special formulas of subculture media designed to overcome bacteriostasis in order to distinguish between the germicidal and the inhibitory action of the various classes of disinfectants which have become available in recent years.

Incidentally, the A. O. A. C. method is being used routinely by a regulatory agency operating under the provisions of the Federal Insecticide, Fungicide and Rodenticide Act; to this extent it enjoys a quasi-legal status.

While the Rideal-Walker method, and its earlier revisions, specified the use of only one test organism, viz., *Salmonella typhosa*, one of the later revisions, viz., the now classical F. D. A. method (of Circular No. 198, published in 1931) set up the requirement for the use of a second microorganism, viz., *Micrococcus pyogenes* var. *aureus*. As viewed in retrospect, the new test organism has been added, not in order to permit a broader evaluation of any given disinfectant, but rather to extend the application of the method to testing antiseptics; evidently, this was done upon the premise that *M. pyogenes* var. *aureus* would be representative of pyogenic and other microorganisms susceptible to control by means of antiseptics, on man or animals. Of course, this was a case of oversimplification since the occurrence of gram-positive microorganisms is not limited to the human or animal body, nor is that of the gram-negative ones limited to the inanimate environment. While the current A. O. A. C. method also specifies both *S. typhosa* and *M. pyogenes* var. *aureus* as test organisms, here the test with the latter organism is supposed to extend the range of information as to the performance of a particular product *as a disinfectant*, rather than as an antiseptic.

Although at one time, test results obtained with *S. typhosa* were considered sufficient for the evaluation of a disinfectant, it has been known for quite some time that this is far from being true. Nevertheless, for a considerable number of years, it has been customary, on the regulatory level referred to, to require that the dilution of a given preparation recommended for general disinfecting purposes shall be such as to correspond in its presumed effect upon *S. typhosa* to a 5

per cent phenol solution. (The latter solution is approximately 4.5 times stronger than the concentration actually germicidal for *S. typhosa* in 10 minutes, viz., 1:90.) This arbitrary requirement was evidently based upon the hypothesis that using a disinfectant solution which is that many times stronger, would give due consideration to a number of safety factors, by way of overcoming certain conditions encountered in practical usage that might interfere with the performance of a disinfectant. Incidentally, a simple method of arriving at this so-called "safe" dilution is multiplying the phenol coefficient of a given disinfectant by the figure 20; the result gives the number of parts of water in which one part of the disinfectant should be dissolved or emulsified, as the case may be.

Thus a disinfectant with a *S. typhosa* phenol coefficient of 5 is to be applied in the form of a 1 per cent solution for general disinfecting purposes, one with a phenol coefficient of 10 in a ½ per cent solution, etc. For the sake of record, it should be pointed out here that whereas the "20 times the phenol coefficient" formula applies to the conversion to the proper use dilution of the data obtained with *S. typhosa*, no comparable rule is provided for the interpretation of the data obtained with *M. pyogenes* var. *aureus*.

The "Use-Dilution" Test

More recently, indications began to multiply that the evaluation of disinfectants by means of the phenol coeffcient method, in addition to being insufficiently informative, also yielded misleading results in several important instances (9). In the case of quaternary ammonium compounds for which extraordinarily high phenol coefficient figures were being claimed, Klarmann and Wright (10, 11), showed that the phenol coefficient method was not the proper procedure for their evaluation; however, a derived method (designated as the "semi-micro" method) permitted better evaluation since it took care of certain peculiarities of these compounds which interfered with the application of the original method. Additional data on this subject were published subsequently by Cade (12), also by McCulloch and associates (13, 14). Eventually official notice was taken of the situation as evidenced by a series of papers (15, 16, 17) culminating, in May 1953, with the publication of supplementary testing procedures by Stuart, Ortenzio and Friedl (18) of the U. S. Department of Agriculture (Pesticide Regulation Section). These new procedures were

designated as "Use-Dilution Confirmation Tests for Results Obtained by Phenol Coefficient Methods"; the authors' point of departure is that "during the last 10 years a rather alarming increase has been noted in the number of commercial products which . . . do not provide adequate margins of safety for disinfection even though they bear apparently valid phenol coefficient claims."

The "Use-Dilution" procedure, differs fundamentally from the several phenol coefficient methods. Whereas the latter consider the effect of disinfectants upon bacteria in suspension, the former employs bacteria deposited on carriers (polished stainless steel rings, "penicillin cups"). The method provides for the use of two test organisms, viz., *S. choleraesuis* and *M. pyogenes* var. *aureus*. (*S. typhosa* is not used in this method because it does not withstand drying on the carriers; incidentally, the resistance to phenol of *S. choleraesuis* and *S. typhosa* is comparable.) The method considers the control of bacteriostasis by expedients which differ with the various classes of disinfectants. Since it requires that any particular recommended use dilution of a given disinfectant shall be capable of killing the test organism in ten replicate tests, it would be too cumbersome to employ directly, i.e., without some preceding exploratory procedure indicating the range of disinfectant concentrations to be tested. Actually, (whether for this reason alone or possibly for some other) it still refers directly to the requirement that the use dilution arrived at by the A. O. A. C. phenol coefficient method (viz., 20 times the phenol coefficient) should be used for general disinfecting purposes, provided that this dilution is germicidal under the conditions of the new test procedure. It should be noted also that the "Use-Dilution" method distinguishes between two general classes of disinfectants, viz., those for "janitorial or household uses", and those for "medical, veterinary, hospital and surgical uses". In the case of the former, *S. choleraesuis* is used as the test organism, in the case of the latter, germicidal potency for both *S. choleraesuis* and *M. pyogenes* var. *aureus* must be established for the recommended use dilution by means of the new test; the professed rationale of the second requirement is that pyogenic microorganisms play an important role in the medical, hospital and surgical areas, and that, therefore, a demonstrable capacity for killing such bacteria must be a prerequisite here.

The following Table I is constructed from the results reported by Stuart, *et. al.* (None of the numbered products tested are identified by their chemical or trade names in the original paper).

TABLE I

RESULTS OF "USE-DILUTION" METHOD (18)

Germicides by type	Phenol Coefficient (*S. typhosa* at 20° C.)	Indicated Use-Dilutions Derived from *S. typhosa* Phenol Coefficients	"Use-dilution" Tests Max. Safe Use-Dilutions (*S. choleraesuis*)	"Use-dilution" Tests Max. Safe Use-Dilutions (*M. pyogenes* var. *aureus*)
Pine Oil				
No. 1	5	1:100	1:100	Undiluted
No. 2	3	1:60	1:60	1:5
No. 3	5	1:100	1:100	Undiluted
No. 4	5	1:100	1:100	1:5
No. 5	4	1:80	1:80	Undiluted
Phenolic emulsifying				
No. 1	5	1:100	1:40	1:20
No. 2	5	1:100	1:100	1:20
No. 3	5	1:100	1:80	1:20
No. 4	5	1:100	1:60	1:5
No. 5	5	1:100	1:40	1:80
No. 6	32	1:640	1:640	1:640
Phenolic soluble				
No. 1	4	1:80	1:80	1:40
No. 2	4	1:80	1:80	1:80
No. 3	5	1:100	1:100	1:80
No. 4	4	1:80	1:80	1:80
Quarternary ammonium				
No. 1	25	1:500	1:100	1:100
No. 2	20	1:400	1:50	1:50
No. 3	25	1:500	None	None
No. 4	5	1:100	1:5	1:5
No. 5	25	1:500	1:60	1:60

Following are the comments on some of these data: As to pine oil disinfectants, it has been known for a long time that they are virtually ineffective against *M. pyogenes* var. *aureus*, and this fact is brought out once again by means of the "Use-Dilution" test. Moreover, since all pine oil disinfectants tested yield a phenol coefficient figure with respect to *S. typhosa* as test organism, one meets here with an instance of the phenol coefficient being entirely non-informative with regard to the breadth of the anti-bacterial spectrum of this class of disinfectants. And lastly, their lack of effectiveness against *M. pyogenes* var. *aureus*, disqualifies them as "medical, veterinary, hospital and surgical disinfectants" for the reason given above.

Only one of the six emulsified phenolic disinfectants tested was found to be effective against both *S. choleraesuis* and *M. pyogenes* var. *aureus* in the dilution derived from its phenol coefficient. Four would have to be used in considerably stronger concentrations if employed as "janitorial or household" disinfectants; however, five to twenty times greater concentrations would have to be employed for hospital and medical purposes, since only such concentrations would be germicidal for *M. pyogenes* var. *aureus*. In the case of the four soluble phenolic disinfectants tested, more consistent results were obtained in regard to the quantitative agreement between the use dilutions derived from the phenol coefficient tests and those found to be effective under the conditions of the "Use-Dilution" tests.

Considerable discrepancies were encountered in the case of quaternary ammonium compounds. None of them was found to be germicidal for either test organism under the conditions of the "Use-Dilution" method, when tested in the concentrations derived from their A. O. A. C. phenol coefficients. With one of the five compounds, disinfection by the confirmatory test method did not result even when the product was used full strength, and this in spite of the fact that the product showed a phenol coefficient of 25 as obtained by the A. O. A. C. test, indicating a presumed capacity for germicidal action in a dilution of 1:500.

Table II gives the results reported by our laboratory with a number of disinfectants available on the market, as obtained by the "Use-Dilution" method. It was found, in the course of these studies, that the numerical significance of the findings could be enhanced by repeating the tests, preferably several times, since in some instances a single test (involving 10 individual readings) did not always yield a clear cut indication of the disinfectant adequacy of a given dilution.

While the results of Table II compare substantially with those of Table I, attention is directed to the results obtained with the "phenolic soluble" preparation No. 6 which shows that in this class too, there may occur formulations of questionable potency with respect to the test conditions of the "Use-Dilution" method.

Validation of the "Use-Dilution" Technique

In order to show the practical applicability of the results obtained by the "Use-Dilution" method, its authors describe two validation procedures relevant to the tests performed with *S. choleraesuis* and with *M. pyogenes* var. *aureus* respectively.

TABLE II

ADDITIONAL "USE-DILUTION" TEST DATA

Germicides by type and active ingredients	Phenol Coefficients Claimed or Found	Indicated or Recommended Use-Dilutions	Dilutions Tested	Number of Tests	*S. choleraesuis* +	*S. choleraesuis* 0	*M. pyogenes* var. *aureus* +	*M. pyogenes* var. *aureus* 0
Pine oil								
(1) Pine oil	—	1:44	1:44	2	0	20	20	0
(2) Pine oil	5	1:44	1:44	2	0	20	20	0
Phenolic emulsifying								
(1) Coal-tar oil	7.5	1:128	1:128	2	1	19	19	1
(2) Coal-tar oil	10	1:88	1:88	4	—	—	38	2
Phenolic soluble								
(1) Phenol, U. S. P.	1	1:20	1:20	5	0	50	0	50
(2) Cresol, U. S. P.	2	1:40	1:40	5	0	50	0	50
(3) Cresylic acid and o-phenylphenol	5	1:100	1:100	5	0	50	1	49
(4) o-Phenylphenol	5	1:100	1:100	5	1	49	1	49
(5) o-Phenylphenol and p-tert. amyl phenol	10	1:200	1:200	5	0	50	1	49
		1:40	1:40	5, 10	1	49	36	64
(6) o-Benzyl-p-chlorophenol and o-phenylphenol	10	1:200	1:200	2	3	17	20	0
Quarternary ammonium								
(1) Benzalkonium chloride	25		1:500	5	13	37	4	46
		1:500	1:200	5	3	47	8	42
			1:100	5	4	46	4	46
(2) Benzethonium chloride	20		1:400	5	14	36	14	36
		1:400	1:200	5	4	46	6	44
			1:100	5	4	46	3	47
(3) Cetyl pyridium chloride	—	—	1:100	5	18	32	9	41

With reference to the former (applying to general disinfection), a chicken excrement suspension, additionally contaminated with *S. choleraesuis*, is spread on a ceramic tile floor; the success of the disinfection is judged by the reduction of the total bacterial count, as well as the elimination of both *E. coli* and *Salmonella*. Reduction of the total bacterial count even to a marked degree, does not necessarily furnish a criterion of elimination of the latter two pathogens; by way of example, a quaternary ammonium compound with an indicated use dilution of 1:100 (as derived from the A. O. A. C. phenol coefficient) reduced the total bacterial count on the floor by over 99 per cent, but only the 1:5 dilution (derived from the "Use-Dilution" test) was effective in killing both the *Salmonella* and the coliform organisms.

The applicability of the "Use-Dilution" technique to the evaluation of disinfectants for surgical instruments and appliances, and involving *M. pyogenes* var. *aureus* as test organism, is validated in a special test procedure which is relevant to the disinfection of surgical instruments. In this case, five typical pyogenic cocci (*Streptococcus pyogenes, faecalis* and *agalactiae*, also *M. pyogenes* var. *aureus* and *albus*) grown on 50 per cent blood broth were used to contaminate scalpel blades.

Table III illustrates the results obtained with an emulsifiable type of disinfectant to which the following information applies:

TABLE III

TESTS OF DISINFECTION OF SURGICAL INSTRUMENTS

	Derived from A.O.A.C. *S. typhosa* Phenol Coefficient	Germicidal for *S. choleraesuis* by "Use-Dilution" Test	Germicidal for *M. pyogenes* var. *aureus* by A.O.A.C. Phenol Coefficient Test	Germicidal for *M. pyogenes aureus* by "Use-Dilution" Test
Dilution	1:000	1:60	1:20	1:5
Organism	Number of blades +	Number of blades +	Number of blades +	Number of blades +
Strep. pyogenes	10	10	0	0
Strep. fecalis	10	9	0	0
Strep. agalactiae	10	2	0	0
M. pyogenes var. *albus*	10	10	10	0
M. pyogenes var. *aureus*	10	10	10	0

A. O. A. C. phenol coefficient 5, derived use dilution 1:100 maximum dilution effective against *S. choleraesuis* (by "Use-Dilution" test) 1:60, maximum dilution effective against *M. pyogenes* var. *aureus* by A. O. A. C. phenol coefficient method 1:20, and the same by "Use-Dilution" test 1:5.

Only the 1:5 dilution is found to produce satisfactory disinfection of the blades in 10 minutes. Neither the A. O. A. C. phenol coefficient, as determined with *S. typhosa,* nor the results obtained by the A. O. A. C. method with *M. pyogenes* var. *aureus* could have served here as a guide in the preparation of a reliably effective solution for the disinfection of surgical instruments.

It would have been gratifying to be able to agree with the implied premise of the "Use-Dilution" method, viz., that the results obtained by this method could be validated, in every instance. Unfortunately, this is not the case. Thus, as has been found in our laboratory, this generalization does not apply to an iodophore type of preparation tested. Here a solution containing 75 ppm of available iodine appears to satisfy the requirements of the "Use-Dilution" test. Yet when applied by the validation procedure as a floor disinfectant, it produces a reduction of the bacterial count of the low order of 55 per cent; moreover, it gives demonstrable evidence of permitting survival of both the *Salmonella* and the coliform types of bacteria. Another deviation is introduced by the comparison of the use dilutions of this iodophore, as derived from the A. O. A. C. phenol coefficient and the "Use-Dilution" tests respectively. As a general rule, the latter dilution is lower (i.e., the concentration is higher) than the former, whereas in the case of the iodophore, the conditions are reversed as illustrated by the figures of 1:44 and 1:213 respectively. By way of supplementary information, the higher concentration of 1:44 produces a better than 90 per cent reduction of the bacterial count in the validation test, but in more than one-half of the tests performed, evidence of survival of *Salmonella* was obtained. It would follow, therefore, that under the conditions of the validation procedure, concentrations higher than 1:44 of this iodophore preparation would have to be employed.

All this is somewhat unfortunate, for obvious reasons. Unless this disturbing feature can be taken care of satisfactorily, further work may have to be done on the regulatory level referred to before, as long as there exists the need for a testing method of universal applicability to all types of products recommended for disinfecting use.

By way of reiteration, the "Use-Dilution" method does not eliminate the A. O. A. C. phenol coefficient test; the latter still continues to remain in force, except that now the dilution figures obtained by the "20 times the phenol coefficient" formula are subject to confirmation by another test.

Perhaps one should mention at this point, for the sake of completeness, that in spite of the wide acceptance in this country and in Great Britain of the original Rideal-Walker testing method and of its several subsequent modifications, the fundamental idea of a suspension test serving for the evaluation of disinfectants has not been, and is not now accepted universally (particularly not on the continent of Europe), and substantially for the reason that in practice, disinfection is not directed, as a rule, against bacteria suspended in a liquid medium, but against those present on solid surfaces. The "Use-Dilution" test while giving due consideration to this principle, does not divorce itself completely from the idea of a suspension test, as evidenced by the direct tie-up between it and the A. O. A. C. phenol coefficient method. It is of possible historical interest that even in England where the Rideal-Walker test method originated, there was no complete unanimity regarding its adequacy, as brought out in a critical paper by Kenwood and Hewlett, as early as in 1906. These authors, incidentally, expressed concern over the insufficient consideration of interference by organic matter with the action of disinfectants. After 50 years, and millions of words that have been both said and written on the subject of the Rideal-Walker technique and of its later modifications, this matter is still open to debate, not only in regard to the problem raised by Kenwood and Hewlett, but also in regard to the general relevance of suspension methods to the practical evaluation of disinfectants. This is not to say, however, that using bacterial suspensions in theoretical studies, e.g., in studying the relationships between the antibacterial potency and the chemical structure of a homologous series of compounds, did not or will not produce valuable background information suitable for subsequent consideration as to its practical applicability; but employing a suspension test as a direct means of determining the practical fitness as a disinfectant of any particular product, is quite another matter.

Presumably, such considerations (in addition to others) prompted Stedman, Kravitz and Bell (19) recently to develop a disinfectant testing procedure employing carriers. The need for a broad-spectrum antimicrobial performance of disinfectants is recognized here by the

requirement for employing three test-organisms representative of pathogenic types, viz., *M. pyogenes* var. *aureus*, *S. schottmulleri*, and *Trichophyton interdigitale*. The technique is known as the "Square Diluent" testing method. It may acquire a quasi-official status in the near future, having been conceived in connection with work on a performance specification for a disinfectant (and fungicide) for use by the U. S. Navy.

Disinfection in Tuberculosis Hygiene

At any rate, the dyad of tests under discussion (i.e., the A. O. A. C. phenol coefficient method and the "Use-Dilution" test) represents still but a screening procedure. As such it is incapable of serving as a substitute for any comprehensive evaluation of a disinfectant which must be based, of course, upon an inquiry into its total antimicrobial spectrum. Precisely in the case of several newer materials such an inquiry is necessary, as it is now known that preparations passing this dyad of tests may not answer the purpose for which they are intended. Reference was made before to the fact that pine oil disinfectants are not of much use against staphylococci. To use another example, in the case of certain quaternary ammonium compounds one may arrive at concentrations promising satisfactory disinfectant performance, yet complete failure will be registered in tests with *Mycobacterium tuberculosis*. To eliminate this dilemma, it has been held occasionally that the term "disinfectant" need not necessarily imply a capacity for tuberculocidal action. One need not concede too readily that this point is well taken. After all, the application of a "disinfectant" is expected to "disinfect", i.e., to cause the destruction of the different types of vegetative pathogens, and not just of some types to the exclusion of others. Conversely, where there is a problem of guarding against any particular type of pathogen, e.g., hemolytic streptococci in a hospital ward, or tubercle bacilli in a TB sanatorium, the application of a product labeled "disinfectant" should not raise any question in the user's mind as to whether the material employed is or is not capable of destroying the microbes against which its use is directed. If this premise is granted, it follows that a "disinfectant", in the true meaning of this term, should be non-specific in action.

With reference to the antitubercular performance of disinfectants, there exist no generally accepted methods of test. While it is held

by the regulatory agency referred to previously that the A. O. A. C. phenol coefficient procedure lends itself for adaptation to tests with *M. tuberculosis* (if supplemented by an *in vivo* challenge test) the question seems justified as to whether or not the experimental conditions of such a test, including the use of a substantially pure culture of *M. tuberculosis*, correspond closely enough to the practical conditions under which this pathogen occurs, protected as it is by sputum in wet or dry form. This is why a test involving the use of active TB sputum deposited on carriers which are subsequently exposed to the action of a disinfectant, is deemed to be more significant than a "phenol coefficient" type of test utilizing tubercle bacilli in suspension, and in the absence of any sputum. Although the test proposed by Frobisher, Sommermeyer and Blackwell (20) refers to the evaluation of disinfectants recommended for use on clinical thermometers, this method, either in its present form or with minor modifications, is considered to be capable of wider application, and particularly in the area of environmental antitubercular sanitation.

Persistence of the "Antibacterial Potential"

An area of inquiry which appears to have been largely neglected is that of the maintenance of an "antibacterial potential" on disinfected surfaces. The usual methods of evaluation of disinfectants, of the type described up to this point concern themselves with the germicidal performance of a given product in comparison with a reference material (e.g., phenol). Reduced to its simplest terms, the test is presumed to furnish the answer to the question as to whether the recommended dilution of a given disinfectant will kill the test organism within a specified period of time; if the finding is expressed in the form of a "phenol coefficient" one will obtain the supplementary information as to how many times more effective the disinfectant under test is than the reference standard, i.e., phenol.

Obviously such information, when properly translated into practical usage, may assure the user of a given disinfectant as to its capacity for the elimination of pathogens from a contaminated surface. However, no information is supplied as to how long the surface will stay "disinfected", or when the disinfectant should be reapplied in order to keep the surface free from pathogens. It is somewhat surprising that this aspect of chemical disinfection appears to have been largely disregarded, particularly if one remembers that, among other things, it is highly pertinent to the problem of the so-called "secondary

reservoirs" of respiratory infection. These reservoirs constitute the sum total of the surfaces, such as floors, walls, furniture, cloths, bedding, etc., upon which pathogens have settled by sedimentation following their dispersal by patients or carriers (often as the result of some form of forced respiratory action, such as sneezing or coughing), and from which they can be redispersed into the environmental air in dry form, as a result of drafts or of some kind of mechanical activity, such as sweeping. Attempts to reduce these "secondary reservoirs" of infectious particles by mechanical fixation (e.g., oiling of surfaces) have not been altogether successful; it would seem that the ideal method of their control should involve the creation upon the surfaces exposed to contamination of an enduring antibacterial potential directed toward the inactivation of such infectious matter. Incidentally, there is reason to believe that these "secondary reservoirs" may be of an even greater significance in the transmission of respiratory illness than direct droplet infection, as from patient or carrier to the healthy individual. The reason is that the great majority of the dispersed infectious particles tends to settle out within a comparatively short period of time while only a small minority remains suspended (after desiccation) in the form of "droplet nuclei". There exists an impressive record of published references to the capacity of many respiratory pathogens (including streptococci, pneumococci, and tubercle bacilli) of surviving in virulent form, and for long periods of time, particularly when protected by dust, lint, etc. It is also known that attempts at disinfection of the environmental air (e.g., by means of germicidal lights, or by aerosolization or vaporization of triethylene glycol, or other chemicals) have not been crowned by success.

Our laboratory published a simple procedure which allows ascertaining the capacity of disinfectants to produce an antibacterial potential on surfaces (21). More elaborate methods requiring special apparatus have been described subsequently by Lester and Dunklin (22), also by Hoffman (23) and by Kaye (24). The results of all these tests indicate that it is feasible, with the aid of suitably formulated disinfectants of stable composition and of a non-volatile character, to maintain such an antibacterial potential on surfaces for days, or even weeks; by contrast, unstable germicides, such as certain hypochlorites, are entirely fugitive in this regard, permitting recontamination of the treated surfaces virtually to the same extent as that of the controls, as early as 30 to 60 minutes after disinfection.

This effect is illustrated in Figure 1 which refers to tests using unglazed porcelain floor tiles as carriers of five pathogenic microorganisms (including a pathogenic fungus). The capacity of the carrier for self-disinfection, as late as one week after the application of a non-volatile synthetic phenolic disinfectant, is in striking contrast to the absence of this quality in the case of a hypochlorite disinfectant applied only 30 minutes prior to recontamination.

Incidentally, the residual antibacterial action produced by the phenolic disinfectant remains virtually undiminished through six daily washes with water.

FIGURE 1

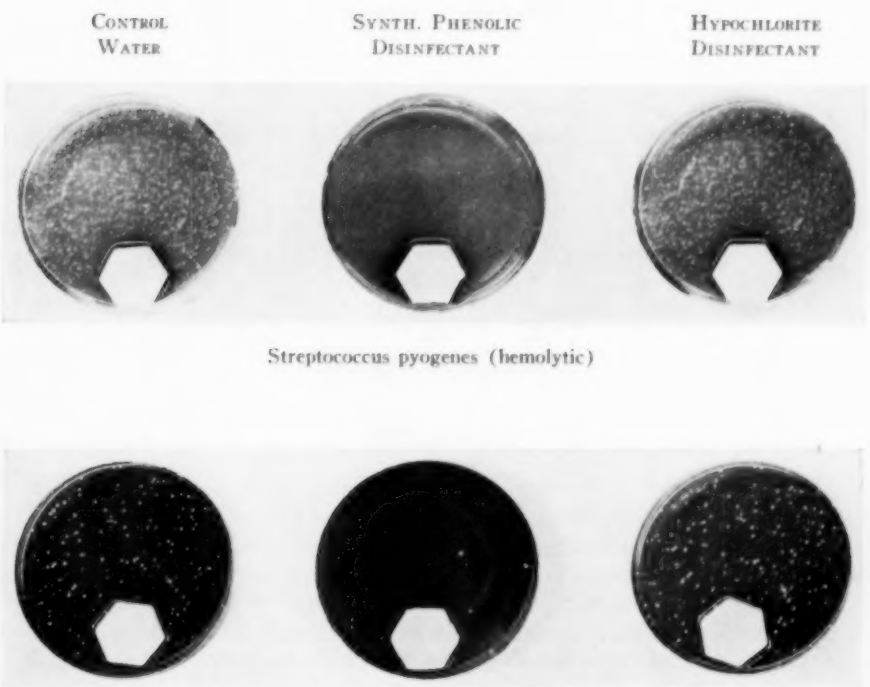

FIGURE 1

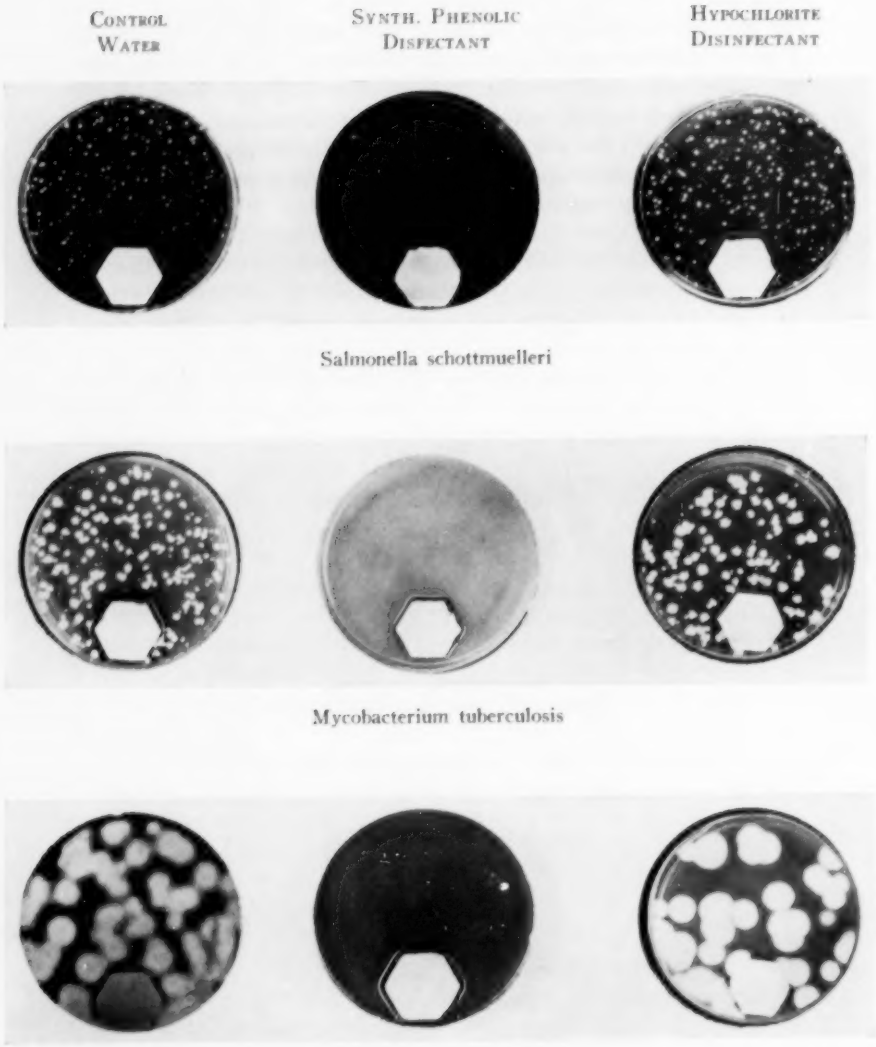
Control Water
Synth. Phenolic Disfectant
Hypochlorite Disinfectant
Salmonella schottmuelleri
Mycobacterium tuberculosis
Trichophyton interdigitale

Figure 2 illustrates the effect of realtive humidity upon the antibacterial potential (with respect to pneumococci) produced by the application of a 1 per cent solution of a synthetic phenolic disinfectant (with o-phenylphenol as active ingredient) as observed by Lester and Dunklin (22). It shows that the maintenance of such a potential is possible as long as the relative humidity does not approach the level of 33 per cent or lower.

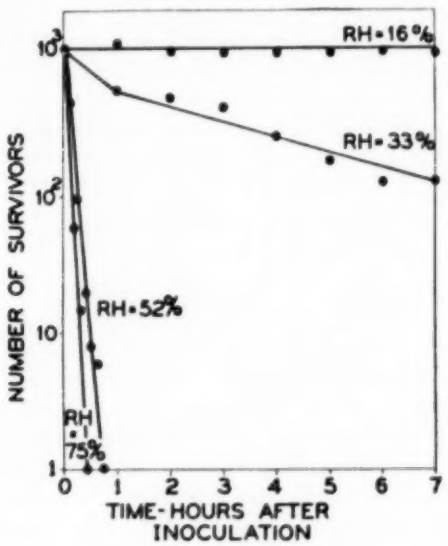

FIGURE 2

The following Table IV summarizes the results obtained with several disinfectants, following a single application to a variety of surface materials. The solutions were allowed to "dry" on the test squares for one week (except in the case of the hypochlorite where the drying period was 2 hours, there being no significant effect in evidence after this period) whereupon the carriers were contaminated with the test organism (*Streptococcus pyogenes*, Lederle 7). At the end of the contact period of one hour the carriers were plated. The counts given are averages of several replicate tests.

TABLE IV

RESIDUAL GERMICIDAL ACTION AGAINST STREPTOCOCCUS PYOGENES ON VARIOUS SURFACE MATERIALS

Disinfectant*	Dilution	Formica			Battleship Linoleum			Asphalt Tile			Rubber Tile		
		(a)+	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Liquor Cresolis Sap. N.F.	1:40	1968	0	100	1520	20	98.7	1500	1155	23	1811	15	99.2
Coal tar type emulsif. (p.c. 7.5)	1:150	1060	26	97.5	1374	33	97.5	1197	900	25	1420	1111	20
Synthetic phenolic (o-phenylphenol p.c. 5)	1:100	716	0.2	100	1370	10	99.3	2126	565	73	1400	80	94
Hypochlorite (5.2% av. Cl.) ..	1:250	1008	1008	0	1162	1540	0	672	872	0	1323	1144	14
Benzalkonium chloride (anhyd.)	1:2500	1480	8	99.5	1449	1134	22	1213	900	25	2080	375	82

Disinfectant*	Dilution	Plastic Tile			Plastic Linoleum			Painted Wood			Shellacked Wood		
		(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)	(a)	(b)	(c)
Liquor Cresolis Sap. N.F. ...	1:40	1260	0	100	325	2.3	99.3	620	714	0	1102	28	97.5
Coal tar type emulsif. (p.c. 7.5)	1:150	1400	82	94	335	6	98.2	620	450	27	930	175	81
Synthetic phenolic (o-phenylphenol p.c.5)	1:100	1417	0.8	100	296	2	99.4	620	222	64	820	187	77
Hypochlorite (5.2% av. Cl.) ..	1:250	1336	820	39	300	400	0	882	633	28	1055	924	12
Benzalkonium chloride (anhyd.)	1:2500	1653	296	82	180	25	86	897	745	16	882	633	28

* Disinfectant drying time one week, except hypochlorite 2 hours. Contact period with microorganism one hour.

+ Average colony counts and percentage reduction: (a) control, (b) test, (c) per cent reduction.

It is quite evident that the type of surface material influences the quantitative aspect of the antibacterial potential to a significant degree. Thus the maintenance of the week long antibacterial potential is most difficult to achieve in the case of painted wood, probably owing to the dissolution of the paint film and penetration of the disinfectant into the wood, as shown particularly by Liquor Cresolis Sap., N. F. which might be expected to exhibit an effective solvent action on paint. It is understandable why completely dense and smooth surfaces such as those of formica, plastic tile, etc. are most satisfactory in regard to the property under discussion. The structure of the surface probably plays a role in the lowered effectiveness of benzalkonium chloride on wood; here possibly a greater adsorptive tendency comes into play in the case of the strongly surface-active agent. The best all around residual performance appears to have been rendered by the synthetic phenolic disinfectant tested.

Significance of Residual Disinfection in Hospital Sanitation

In this general connection, it is possible that the establishment of a sanitary environment in hospitals, by maintaining an enduring antibacterial potential on disinfected surfaces, will be recognized as one important step toward the reduction of incidence of staphylococcal sepsis which lately has become a vexing problem in hospital practice (and which may have been aggravated by the emergence of antibiotic-resistant strains of staphylococci, conceivably due to a somewhat indiscriminate reliance upon broad-spectrum antibiotics, with a concomitant lack of proper attention to environmental sanitation). This possibility is further suggested by certain experimental findings (made at the University of Chicago Medical School) by Lester and Dunklin [1] which are referred to here because they tend to support the proposition as to the inadequacy of the customary testing methods with respect to the disclosure of some important properties shown by certain disinfectants.

These authors demonstrated previously (*22*) that the residual disinfectant action exhibited by surfaces treated with a particular synthetic phenolic disinfectant ("O-syl") was in evidence against the naturally present dust borne microorganisms, as well as against spray-dried pneumococci and streptococci. Their most recent study is in the nature of a field experiment in a logical environment, viz., in the recovery room of a surgical department; it indicates that as a result

1. Personal communication, to be published.

of regular, daily application of this disinfectant to the floor of the recovery room (and entrance hall), it was possible to reduce the bacterial counts to a very marked degree not only on this surface, but also in the environmental air.

Thus the over-all reduction in the bacterial contamination of the floor averaged more than 95 per cent even though it was in use regularly, with new contamination being introduced continually by physicians, nurses and attendants. Air sampling indicated a depression of the bacterial count of the atmosphere by some 60 to 80 per cent. It is noteworthy that even untreated surfaces (shelves) showed a markedly reduced bacterial count, no doubt owing to a lowered bacterial contamination of the environmental air which, in turn, was due largely to the decontamination of the floor area.

In agreement with these observations is the report by Seal (47) on the reduction of streptococcal infection in a military dormitory, resulting from the application of a synthetic phenolic disinfectant to floors and other surfaces, also to blankets and bedding, with the view to controlling environmental transmission of respiratory infection.

Again, it is emphasized that these significant findings could not have been obtained with any of the usual testing methods which, therefore, cannot furnish any information as to whether a given disinfectant is or is not capable of imparting a persistent antibacterial potential to disinfected surfaces, with all of the desirable sequelae of such treatment, not only in the operating room area, but also elsewhere as an aid in reducing the incidence of infections and cross-infections transmitted through the medium of the environment.

To be concluded in next issue (Ed.)

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ABSORPTION OF TRYPSIN FROM THE BUCCAL POUCH

By R. Brendel, J. M. Beiler, and G. J. Martin *

ADMINISTRATION of small quantities of trypsin to animals and humans is known to produce marked systemic effects which are of interest from both the laboratory and clinical standpoints. These effects are manifested when trypsin is administered by the intravenous, intramuscular, subcutaneous or intraperitoneal routes (1, 2, 3).

Trypsin produces an increase in tissue permeability which is correlated with its antiphlogistic effect (4). It is known as well to facilitate passage through tissue of normally impenetrant substances (5). These actions suggested that, despite its large molecular size, trypsin might cause sufficient increase in permeability in some of the readily accessible mesodermal tissues of the body to facilitate its own absorption. In view of the widespread clinical use of trypsin and the necessity for the use of injection techniques in its administration, this possibility seemed of sufficient importance to warrant investigation.

Experimental

The buccal membrane was chosen for study because of its accessibility and the relative ease of administration of substances clinically by the buccal route. Clinical effectiveness of trypsin administered by this route has been reported (6). Absorption of trypsin was measured by its inhibitory effect on the production of egg-white edema in rats. The animals (about 100 gm. in weight) were anesthetized with pentobarbital 50 mg/k I. P. When the anesthesia was deep enough so that the swallowing reflex was inhibited they were laid on their sides and trypsin at the various doses used in 0.25 ml. of saline was dropped into the buccal pouch. After one hour 0.1 ml. of egg-white was injected into one hind leg and 0.1 ml. of saline into the other. Determination of the extent of the edema was carried out by weighing the two hind legs 1.5 hours later as previously reported (2).

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The difference in weight between the egg-white and saline-injected legs was taken as representing the extent of the edema. Controls were treated in the same manner except for the omission of trypsin.

Results

Results are presented in Table I. Figures are averages for groups of five animals in each case, and represent the weight differences between the control legs injected with saline and the edematous legs treated with egg-white. The groups were matched in weight, and there was a difference of only ten per cent between the extremes of the average weights of the control legs for each group.

TABLE I

INHIBITION OF EGG-WHITE EDEMA IN RATS BY BUCCALLY-ADMINISTERED TRYPSIN

Dose Trypsin (mg/k)	*Weight Difference (gm.) Edematous Leg-Control Leg*	*Inhibition of Edema (per cent)*
Control	1.94 ± .11	—
20	0.80 ± .12	55
10	1.46 ± .08	25
5	1.82 ± .21	0
2	2.02 ± .06	0
Control	1.80 ± .16	0

Discussion

The results show a significant reduction of edema by the buccally-administered trypsin. The minimum effective dose, 10 mg/k, is somewhat higher than that found on subcutaneous injection (2). Differences in rates of absorption probably account for this.

Although inhibition of egg-white edema was chosen as the most convenient method for measuring the systemic effects of trypsin, these can be demonstrated by other methods after buccal administration of the enzyme. For example, the area of spread of intracutaneously-injected india ink in rabbits was found to be increased 100 per cent over control values in animals given trypsin buccally; this same effect is obtained on parenteral administration of the enzyme (4). As might be expected, absorption is not confined to the buccal membrane. Sig-

nificant inhibition of egg-white edema was obtained when trypsin was given intravaginally in a carbowax-based tablet, showing absorption from this site.

The demonstration that trypsin is absorbed from the buccal pouch would appear to be of marked importance clinically. Removal of the necessity for the use of injection techniques should facilitate greatly the therapeutic use of the enzyme.

Summary

Buccally-administered trypsin has been found to inhibit the development of egg-white edema in rats, showing that the enzyme is absorbed from this site.

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SELECTED ABSTRACTS

Studies of Lignocaine Hydrochloride and Its Solutions. Bullock, K., and Grundy, J. *J. Pharm. Pharmacol. 7*:755 (1955). Lignocaine hydrochloride is a local anesthetic having a potency similar to that of procaine hydrochloride. Most local anesthetics are relatively easily hydrolyzed in solution, particularly at pH values above 7. However, the lignocaine molecule is highly resistant to hydrolysis by both acid and alkali. It has been shown recently that local anesthetics in buffered alkaline solutions are superior for dental surgery. It is thought that the local anesthetic base must dissolve in fatty tissue and that the liberated acid from the compound must be neutralized so that the pH of the tissue site will not be lowered. The latter would result in a decreased supply of the anesthetic base. An alkaline buffer solution would aid by neutralizing the liberated acid. Therefore, if stable alkaline solutions of lignocaine hydrochloride could be prepared they might prove to be superior to other local anesthetics.

The authors discussed the synthesis and purification of the compound as well as its assay. Several assay methods were found to be reasonably satisfactory. The most convenient method was titration of the excess acid added to the base with standard alkali using bromcresol green as the indicator. A test was also developed which would detect less than 0.1 per cent of decomposition in a 2 per cent solution of lignocaine hydrochloride. This was then applied to studies of the stability of 2 per cent solutions of lignocaine hydrochloride under the usual conditions of preparation, sterilization and storage.

Studies on the stability of 6 different solutions containing 2 per cent of lignocaine hydrochloride with sodium chloride, disodium phosphate, and/or monosodium phosphate were undertaken. All were made isotonic and the amounts of the buffer salts were varied to give solutions having a pH of 7.0, 7.1, 7.2, 7.3, 7.5 and 4.8. The latter contained only lignocaine hydrochloride and sodium chloride. A 2 per cent solution of anhydrous lignocaine hydrochloride was found to have a freezing point depression of 0.278° C. All six of these solutions proved to be remarkably stable. Autoclaving at 115° C. for as

long as 3 hours or storage at room temperature for over 18 months brought about less than 0.1 per cent decomposition. During autoclaving an oily layer of lignocaine base appeared on the surface of the more alkaline solutions. However, with occasional shaking during cooling this redissolved to from a perfectly clear solution. The pharmacological activity and clinical suitability of these solutions are being studied.

A New Series of Analgesic Compounds. Grossman, A. J., Golbey, M., Gittinger, W. C., and Batterman, R. C. *J. Am. Geriat. Soc. 4*:187 (1956). A new series of analgesic compounds was investigated. They possessed a seven-membered ring in place of the six-membered ring as found in meperidine. The compound 1-methyl-4-carbethoxy-4-phenylhexamethyl-enimine (Wy-401) and two of its derivatives were tested in human subjects. They had previously shown promise in tests in animals.

The compound designated as Wy-401 was found to be preferred at the time the data was presented. The results from the other two had not been fully evaluated nor an optimum dosage established.

Initially, the dosage of compound Wy-401 employed was 250 mg. four times a day. A high incidence of toxic reactions required the dosage to gradually be reduced until 50 mg. four times a day was selected as optimum. At this dosage level only 2 of 38 patients experienced toxic reactions. The manifestation encountered was slight nausea in one and anorexia in the other.

At the 50 mg. dosage level 27 of 38 patients (71 per cent) had satisfactory analgesia. The patients had experienced pain from a variety of conditions, including cancer. The authors reported that the results indicated that oral Wy-401 was more potent than codeine and considerably less toxic.

The tendency of this compound to cause addiction was tested by continuing the administration of 75 mg. four times a day to 12 patients who had shown no toxic reactions to this dosage level. Six of these received the drug for 11 to 18 weeks and six received it for six months. No withdrawal symptoms were observed in any of the twelve patients.

Parenterally, it was found that the dosage form then available was unsatisfactory because it was a racemic mixture, and that the dextro and levo forms possessed mutually antagonistic properties.

The Treatment of Epilepsy with Acetazolamide. Ansell, B., and Clarke, E. *Brit. Med. J. 4968:*650 (1956). On the basis of its ability to produce an acidosis, acetazolamide (Diamox) was evaluated for its anticonvulsant properties in epilepsy. Twenty-six patients were treated, 23 of whom had the idiopathic type of epilepsy. A dose of 125 mg. of acetazolamide twice a day was added to the previous medication, initially. If improvement occurred and was sustained, the other drugs were gradually eliminated. If no benefit was obtained, the dose was gradually increased until as much as 10 mg. per. Kg. of body weight was given.

Excellent results were obtained in 8 patients, good in 6, some improvement in 8 and no improvement in 4 patients. Excellent results were defined as complete freedom from attacks, good as a marked decrease in frequency, and some value as an initial reduction in the number of attacks with a return to the pre-treatment level in one or two months. The authors concluded that acetazolamide may be of value as the sole therapeutic agent in the treatment of major epilepsy, in some cases of minimal epilepsy, and as adjuvant therapy in mixed idiopathic epilepsy.

The mode of action of the drug is not known. However, in continued dosage it did not appear to be depend upon the production of a systemic acidosis or on its diuretic effect. When given at the time of the menses, it was felt that its beneficial effect might be related to the diuresis. The suggestion was made that it may act specifically on the carbonic anhydrase in the epileptic brain.

Laboratory and Clinical Studies with Nystatin. Stewart, G. T., *Brit. Med. J. 4968:*658 (1956). Laboratory studies indicated that nystatin was unstable in aqueous suspension or in solution in organic solvents. A sharp fall in antifungal activity against liquid cultures after 18 to 24 hours was thus observed. An aqueous suspension kept at —20° C. retained full potency for two weeks but losses of up to 50 per cent potency occurred in less than 7 days in solutions and suspensions kept in the dark at room temperature and at 37° C.

Various carbohydrate and alcoholic substances were found to affect nystatin differently. The presence of a chain of CH_2 groups, as in alcohols, favored activity, while CHOH and CHO groups, as in various sugars, were antagonistic. Glycols, with a combination

of both, showed intermediate properties. The author suggested that the presence of glucose and other substances in the blood stream might affect the activity of nystatin.

The exposure of *Candida albicans* and *Saccharomyces cerevisiae* to sub-inhibitory and fully inhibitory concentrations of nystatin *in vitro* disclosed no tendency on the part of the surviving organisms to acquire resistance. Nystatin showed no effect *in vitro* against various strains of streptococci, staphylococci, and coliform bacteria but was effective against the test fungus strains in the presence of these bacteria. Also, the presence of nystatin did not interfere with the action of penicillin, the tetracyclines, chloramphenicol or streptomycin against organisms sensitive to these antibiotics.

A therapeutic trial of nystatin against mycotic infections in 22 patients showed rapid and complete clearance of the infection in 16 and temporary clearance in 4. No toxic side effects were observed with the exception of transient nausea. However, when nystatin was given along with antibiotics in an attempt to prevent mycotic superinfections, it was not successful.

The Formulation and Testing of Silicone Vanishing Barrier Creams. Plein, J. B., and Plein, E. M. *Bull. Am. Soc. Hosp. Pharm. 13:*38 (1956). Because of the cosmetic acceptability of vanishing type creams, the authors prepared a series of twelve different silicone vanishing creams. These were compared with three commercial silicone ointments, one commercial silicone lotion, white petrolatum and wool fat as to their protective effectiveness. An *in vitro* and an *in vivo* test method was developed.

The *in vitro* test method consisted in a measurement of the malachite green given up to distilled water after six hours by applicator sticks previously dipped in malachite green solution and dried. The sticks were coated with a measured quantity of the test cream or ointment before being placed in the water.

The *in vivo* test method consisted in an evaluation of the color developed by a drop of soluble starch solution when placed upon a dried stain of strong iodine solution on the forearm. The stain of iodine had been covered with a measured quantity of the protective preparation. Both the time required for color to develop and the intensity of the color remaining after the excess starch solution was blotted off, were used to evaluate the effectiveness.

The following vanishing cream was rated first by the *in vivo* test and fifth by the *in vitro* test for protective effectiveness:

Stearic acid (Pearlstearic)	10.0
Synthetic Japan Wax	2.0
DC 200, 1000 cts.	20.0
Potassium hydroxide	0.5
Methylparaben	0.025
Propylparaben	0.015
Distilled Water	67.5

The quantities are given in terms of percentage by weight.

The Prenatal Diagnosis of Sex on the Basis of Chromocenter Cells. Sachs, L., Serr, D. M., and Danon, M. *Science 123*:548 (1956). It has been shown that there is a higher percentage of chromocenter cells in females than in males in a variety of tissue in human beings. The authors tested for the possibility of the presence of these cells in prenatal amniotic fluid as a basis for diagnosis of the sex of the fetus. They found that these cells were present in the human amniotic fluid. In 35 tests conducted during the ninth month of pregnancy, the correct sex of all of the fetuses was diagnosed. A few tests performed on the amniotic fluid during the sixth and the seventh months showed that sufficient cells were also present at these stages to diagnose the sex of the fetus.

They also found that suitable cells were present in the fluid of an aborted 8-week-old human embryo to diagnose the sex.

The Treatment of Hypertension with Antihistamine. Lipman, D. G. *J. Am. Geriat. Soc. 4*:286 (1956). The author presented a preliminary report of the use of an antihistamine, chlorprophenpyridamine maleate, in the treatment of 16 patients with hypertension. The drug was given in the form of repeat action tablets of 8 mg. strength. Initially one tablet was given every 8 hours. For maintenance, some patients required one tablet every 8 to 12 hours while others were satisfactorily controlled with one tablet every 24 hours. All of the patients had proved to be refractory to previously prescribed therapy. The average duration of the hypertension was 9½ years.

All of the patients showed a definite clinical improvement associated with a drop in both the systolic and diastolic blood pressures.

Two patients died of complications not related to the therapy. Nine of the remaining 14 patients showed a satisfactory clinical response to chlorprophenpyridamine maleate therapy. Three of the 14 patients responded to concomitant use of hypotensive drugs to which they had previously been resistant. The other 2 patients showed only a very limited response. The average duration of treatment was twelve months.

Therapy with Reserpine in the Aged. Smigel, J. O., and Murphy, C. *J. Am. Geriat. Soc. 4:260* (1956). The effect of therapy with reserpine in 60 elderly patients with hypertension was reported by the authors. Reserpine (Serpasil) was administered to about one-half of the patients in a dose of 0.5 mg. twice a day for six months. Rauwolfia (Raudixin) was administered to the other one-half of the patients in a dose of 50 mg. twice a day. After about 3 months of therapy with the whole root preparation, reserpine was given instead. The age of the patients ranged from about 42 to 88 years.

The average systolic blood pressure of the 60 patients at the beginning of treatment was 187 and the diastolic was 101. After six months of therapy, the average systolic pressure had dropped to 148 and the average diastolic to 76. Among ten of the patients who were out-patients the reduction was more striking than the over-all average. Their initial average was 210/106 but after treatment for six months it was 156/83. The pulse rate was reduced by an average of 12 beats per minute. It was felt that this was not simply an alteration of the rate but an alteration of the action of cardiac muscle associated with over-stimulation of the nervous system affecting the heart.

Even more striking results were observed in the mood of the patients. A calmness settled over the patients after a few days of therapy. Not only was physical deterioration retarded but also the advance of mental dissolution. Confusion and disorientation was replaced by practically normal realizations of environment in many cases.

Side effects were relatively mild. Stuffiness of the nose occurred occasionally but was controlled by antihistamines. Occasionally headaches occurred. On the other hand, headaches were eliminated from the initial symptoms of some patients. Neither nausea nor diarrhea occurred.

BOOK REVIEWS

The Systematic Identification of Organic Compounds. By Ralph L. Shriner, Reynold C. Fuson and David Y. Curtin. Fourth edition. v + 426 pp., 1956. John Wiley and Sons, Inc., 440 Fourth Ave., New York 16, N. Y. Price $6.00.

This is the latest revision of the excellent organic textbook that has justly become a standard for most courses in qualitative organic analysis. The authors have maintained their direct and clearly written approach to the problems of identifying functional groups of organic compounds. This book contains many important additions and improvements on the previous editions. One outstanding feature is the chapter on the use of infra red and ultra violet spectroscopy for functional group determination. The use of chemical literature and of various physical techniques, such as melting point determinations, have been greatly emphasized, while theoretical discussions have been enlarged and modernized.

A. R. GENNARO

Pomp and Pestilence. By Ronald Hare. Philosophical Library, 15 East 40th Street, New York, N. Y., 1955. 224 pages. 5 x 8 x ¾".

A most delightful and well presented resume of man and his history of disease is seen in this book. It is very informative and written in a style easy to read and digest. In addition to Acknowledgments, there are seven chapters: Parasites and Parasitism, Man and His Parasites, Parasites and Pestilence, Miasms or Microbes, The Reaction of the Community, The Reaction of the Individual and, Parasites and Populations. There is a section of Notes and References and a well compiled Index.

This book will well take its place among the compilations of man's pestilence and the various methods which have gradually been evolved by which infectious diseases may be controlled or their lethal powers diminished.

BERNARD WITLIN

Methoden Der Organischen Chemie (Houben Weyl), Vol. 3., Part 2. Physikalische Methoden. E. Müller. G. Thieme, Stuttgart 1955. XXVIII, 1078 pp. 507 Illus. DM 186, $44.30.

Physical methods, as the editors of this handbook of methods of organic chemistry justly state, have become increasingly important for the preparative organic chemist. This volume on physical methods is a comprehensive review of the most important physical methods (theory, application and apparatus) useful to the organic chemist. The 18 contributors of the 21 selected chapters cover a wide field and wisely restrict discussion of the techniques, which belong in the hands of the physicist or physical chemist, to the essentials. Thus such important methods as x-ray absorption spectroscopy, x-ray diffraction, and microwave spectroscopy are only described to the extent necessary to familiarize the organic chemist with the theoretical basis and the principal apparatus required for such studies. Absorption spectroscopy in the visible and ultraviolet range which is indispensable to every organic chemist, on the other hand is covered in almost monographic form. This chapter, which gives also about 250 spectra and their interpretation is the most comprehensive of the volume and probably one of the most concisely written chapters on this subject in the available literature. Infrared spectroscopy, and Raman spectroscopy are covered as well as they can be covered in 106 and 30 pages respectively. The chapters on polarography, light scattering, quantitative electrophoresis, fluorescence and phosphorescence, pH determination, potentiometric and conductometric titration, and other chapters not mentioned in this review are equally well written. The book does not claim to describe all the methods. It is felt, however, that mass spectrometry should have been mentioned briefly, although it concerns more the analytical than the preparative organic chemist. The list of references to 1954 is comprehensive. The illustrations are excellent. The publisher, the editor, and the contributors alike should be congratulated on this excellent book which will be most welcome to the organic chemist.

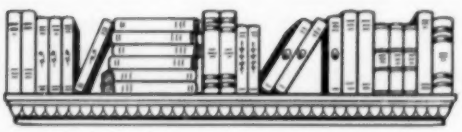
Henry P. Schwarz,
Philadelphia General Hospital,
Philadelphia, Pennsylvania.

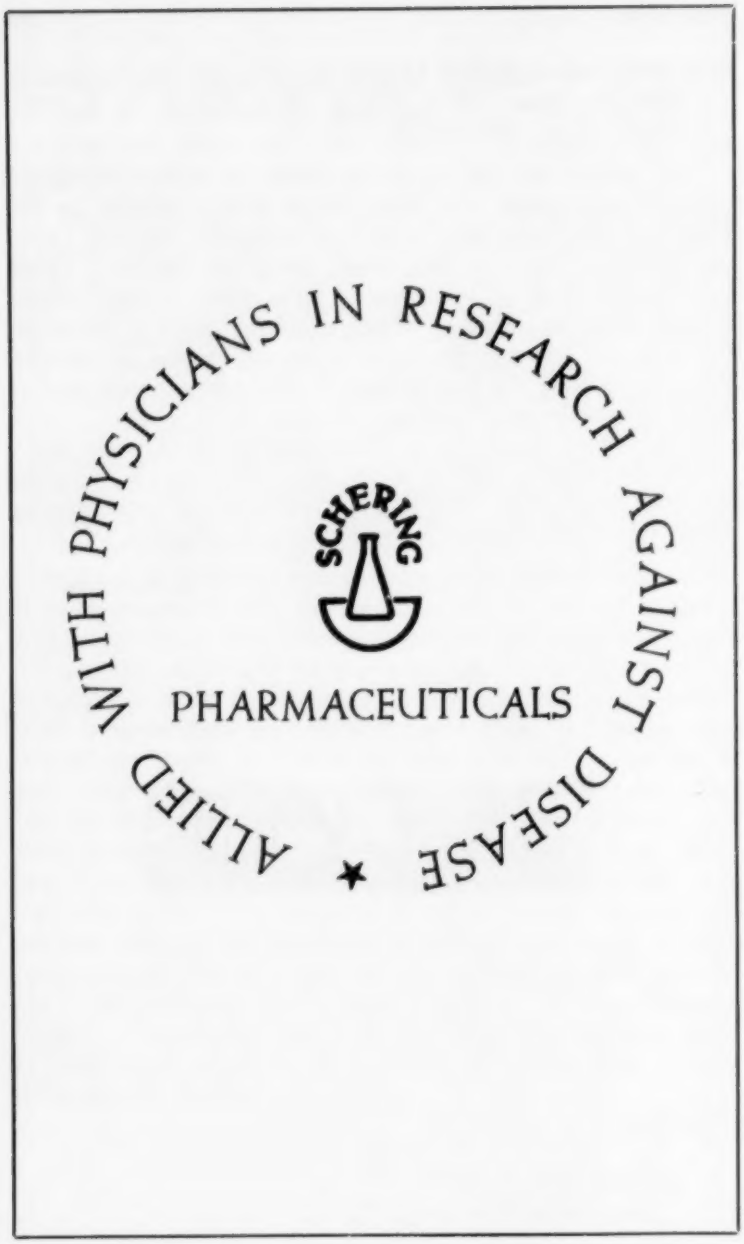
From Classical to Modern Chemistry. A. J. Berry. Cambridge University Press. 32 E. 57th St., New York 22, N. Y., 1954. xii + 251 pp. Price $4.75.

Dr. Berry's new addition to the history of chemistry is indeed very pleasant reading. The book consists of nine chapters on The Theory of Chemistry, Heat, Aspects of Electricity, Physical Optics and Chemistry, Molecular Magnitudes, Analytical Chemistry, Chemical Formulas, Valency and Kinetics. The history of each subject is traced from the beginning of each established phase of chemistry. Especially interesting to the reviewer was the chapter on Chemical Formulas, relating the development of the modern system used to designate formulas and equations.

Each chapter is concluded with a long list of references and a selected bibliography appears at the end. There is also a subject and name index. It is surprising how much can be learned reading a book such as this supposedly for pleasure and relaxation.

A. R. GENNARO

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